Mucosal healing with anti-TNF antibodies

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Key Words
Mucosal healing · Crohn's disease · Ulcerative colitis · Endoscopic indices

Abstract
Nowadays, mucosal healing is regarded as a major end point in clinical trials and is increasingly used in clinical practice for the management of patients with inflammatory bowel disease. The definition of mucosal healing varies across studies and validated endoscopic scoring indices are still lacking. The advent of anti-tumor necrosis factor agents has changed the way of treating inflammatory bowel disease and high rates of induction and maintenance of mucosal healing can be achieved with this drug class. Mucosal healing is desirable as it may change the natural course of the disease by decreasing surgery and hospitalization rates in both ulcerative colitis and Crohn's disease.

The initial lack of a correlation between mucosal healing (MH) and clinical remission in patients with inflammatory bowel disease (IBD) led clinicians to abandon this concept [1]. The advent of anti-tumor necrosis factor (anti-TNF) agents has changed the way of treating IBD. Anti-TNF therapy allows not only a rapid improvement of symptoms, but also MH [2]. Accumulating evidence indicates that MH may change the course of both Crohn's disease (CD) and ulcerative colitis (UC) [3–5]. Accordingly, MH is now regarded as an important treatment end point in clinical trials and is increasingly used in the clinical management of IBD [6].

After discussing current definitions of MH, we will review the efficacy of anti-TNF antibodies in inducing and maintaining MH, and then highlight the positive impact of MH on long-term outcomes in IBD.

Defining Mucosal Healing

MH is usually assessed by ileocolonoscopy or proctosigmoidoscopy in CD and UC, respectively. However, the definition of MH varies across studies and there is no validated definition of MH or endoscopic remission in IBD [7, 8]. Various definitions have been used in CD in clinical trials and referral-center-based studies (table 1, 2): the absence of mucosal ulcerations and ulcers [9, 10] or the absence of ulcerations at follow-up endoscopy in patients in whom ulcerations were present at

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Table 1. Main clinical trials with anti-TNF agents using MH as a primary or secondary end point in CD

Study name [ref.]	Study design	Anti-TNF agent	Endoscopic index used	MH definition
ACCENT 1 (endoscopic substudy) [10]	multicenter, randomized, double-blind, controlled study	infliximab	CDEIS	complete absence of mucosal ulcerations that were observed at baseline
SONIC [24]	multicenter, randomized, double-blind, controlled study	infliximab	No score used - only a descriptive evaluation	complete absence of mucosal ulceration in the colon and terminal ileum
D'Haens et al. [30]	multicenter, open-label, randomized study	infliximab	SES-CD	no ulcers
MUSIC [16]	multicenter, open-label study	certolizumab	CDEIS	absence of ulcers; endoscopic remission defined as CDEIS <6
EXTEND [9]	randomized, double blind, placebo-controlled study	adalimumab	SES-CD	absence of mucosal ulceration

baseline ileocolonoscopy [11]. The definition of MH in CD as the total disappearance of ulcers is simple in clinical practice, but this binary statement does not take into account patients with evidence of MH under treatment with some remaining lesions, like erosions. For UC, the International Organization of IBD made a consensus in 2007 to define MH: the absence of friability, blood, erosions and ulcers in all visualized segments of the gut mucosa [12]. Presence of abnormal vascular pattern is compatible with MH according to panel experts [12].

For the assessment of MH, clinicians require reproducible and validated scoring indices of disease activity (table 1) [12]. There are three main endoscopic disease activity indices used in clinical trials for CD: the Crohn's Disease Endoscopic Index of Severity (CDEIS) [13], the Simple Endoscopic Score for Crohn's Disease (SES-CD) [14] and the Rutgeerts score [15]. The CDEIS is a prospectively built scoring index, based on elementary CD lesions and the percentage of involvement of different ileocolonic segments [13]. The CDEIS, considered as the gold standard scoring index, is regarded as complex and this limits its usefulness in clinical practice, largely restricting it to the clinical trial setting. A simple index, the SES-CD has been developed and correlates well with the CDEIS [14]. SES-CD involves four variables: ulcer size, the extent of the ulcerated surface, the extent of the affected surface and stenosis in five bowel segments. However, the SES-CD is not validated. For both indices, there is no validated cut-off value for defining endoscopic remission, response or MH. Two cut-offs defining endoscopic remission (CDEIS <6) and complete MH (CDEIS <4) have been proposed [16].

The Rutgeerts score is used in the postoperative setting to determine the presence and severity of endoscopic disease recurrence in the neoterminal ileum after ileal or ileocolonic resection [9]. Scoring is based on the presence of aphthous lesions, inflamed mucosa, nodules and narrowing, and ranges from i0 to i4 accordingly [9]. Most clinical trials have used i2 as a cut-off to define endoscopic recurrence. However, the Rutgeerts score still lacks validation.

In the small bowel, capsule endoscopy is increasingly used to assess the severity of CD [17]. Specific disease activity indices have been developed, but still await validation before using them in clinical trials and/or clinical practice [18].

For UC, the first index was developed by Truelove and Witts [19] in a placebo-controlled trial on cortisone treatment. Thereafter, several endoscopic system scoring systems have been developed (e.g. the modified Baron score [20] and the Mayo endoscopic subscore [21]) but none of them have been fully validated (table 2). Recently, Travis et al. [22] proposed a new endoscopic score, namely the Ulcerative Colitis Endoscopic Index of Severity. Development of this index was made in two phases in order to assess intra- and inter-individual variation in the overall endoscopic assessment of severity [22]. One of the major differences with the Mayo endoscopic subscore is the exclusion of the item 'friability' from the endoscopic description of severity [22]. This score is composed of the following items: vascular pattern, bleeding, erosions and

Table 2. Main clinical trials with anti-TNF agents using MH as a secondary end point in UC

Study name [ref.]	Study design	Anti-TNF agent	Endoscopic index used	MH definition
ACT-1 [25]	multicenter, randomized, double-blind, placebo-controlled study	infliximab	Mayo endoscopic subscore	absolute subscore for endoscopy of 0 or 1
Afif et al. [27]	multicenter, open-label study	adalimumab	Mayo endoscopic subscore	decrease in endoscopic subscore from 2 or 3 at baseline to 0 or 1
ULTRA 2 [28]	multicenter, randomized, double-blind, placebo-controlled trial	adalimumab	Mayo endoscopic subscore	endoscopy subscore 0 or 1

ulcers; once it has been validated independently, it should be used mainly in clinical trials and clinical practice in the future [22].

Induction and Maintenance of Mucosal Healing with Anti-TNF Agents

Induction

In the ACCENT 1 [23] trial, a randomized controlled trial evaluating the efficacy of infliximab for the treatment of refractory active CD, an endoscopic substudy [10] of 99 patients was performed. MH was observed at week 10 in 29% of patients (13/45) who had received induction therapy with three infusions of infliximab compared with 3% of patients (1/29, $p = 0.006$) who had received only one infusion at baseline [10]. Systematic maintenance therapy with infliximab therapy every 8 weeks allowed MH in 44% (16/36) of CD patients at week 54 compared to 18% (4/22, $p = 0.041$) in patients treated episodically [10]. In the SONIC trial, which compared infliximab monotherapy, azathioprine monotherapy and combined infliximab and azathioprine therapy for active luminal CD, MH was significantly higher in the combined arm (44%, $p < 0.001$) at week 26 [24].

The MUSIC trial is an open-label study that assessed the ability of certolizumab pegol to induce MH at 10 weeks in 89 CD patients with active disease [16]. Induction therapy consisted of subcutaneous injection at weeks 0, 2 and 4 followed by 1 injection at week 8. At 10 weeks, endoscopic remission (defined as CDEIS <6) was seen in 42%, but MH (defined as an absence of ulcers) was seen in only 5% of patients [16]. The EXTEND trial, evaluating the efficacy of adalimumab for the treatment of moderate to severe active ileocolonic CD, used MH at week 12 as a primary end point [9]. One hundred and thirty-five CD patients received 160-mg and 80-mg induction therapy at weeks 0 and 2, respectively, and were then randomized at week 4 to blinded maintenance therapy with 40 mg adalimumab every other week or placebo up to week 52. The primary end point was achieved in 27% (17/62) of the adalimumab arm compared with 13% (8/61) of the placebo-treated patients ($p = 0.056$) [9]. At week 52, rates of MH were 24% and 0, respectively ($p < 0.001$). Remission rates, based on CDEIS, were 52% for adalimumab and 28% for placebo at week 12 ($p = 0.06$) and 28 and 3%, respectively, at week 52 ($p < 0.01$) [9] (fig. 1).

In the ACT-1 and ACT-2 trials (Active Ulcerative Colitis Trials 1 and 2), [25, 26] infliximab or placebo were administered intravenously in 364 (in each study) patients with moderate to severe refractory UC. Induction therapy with infliximab 5 mg/kg given at weeks 0, 2 and 6 resulted at week 8 in MH in 62% of patients in the ACT-1 trial and in 60.3% of patients in ACT-2 compared with 33.9 and 30.9% in the placebo groups of each study ($p < 0.001$ in both trials) [25, 26]. A small, open-label study involving 20 patients evaluated the efficacy of adalimumab in patients with endoscopic evidence of active, moderate to severe, refractory UC [27]. Induction treatment with adalimumab 160 mg at week 0, 80 mg at week 2 and 40 mg every other week resulted in MH in 30% of patients at week 8 [27]. Finally, in the ULTRA 2 trial [28], a randomized, double-blind, placebo-controlled trial, the efficacy of adalimumab in UC patients for induction was evaluated [28]. At week 8, MH was achieved in 41.1% of patients receiving adalimumab and 31.7% of patients receiving placebo ($p = 0.032$) [28] (fig. 2).

Maintenance

Anti-TNF agents have also demonstrated efficacy in maintaining MH in IBD patients. In the ACCENT 1 trial [23], scheduled treatment strategy with infliximab

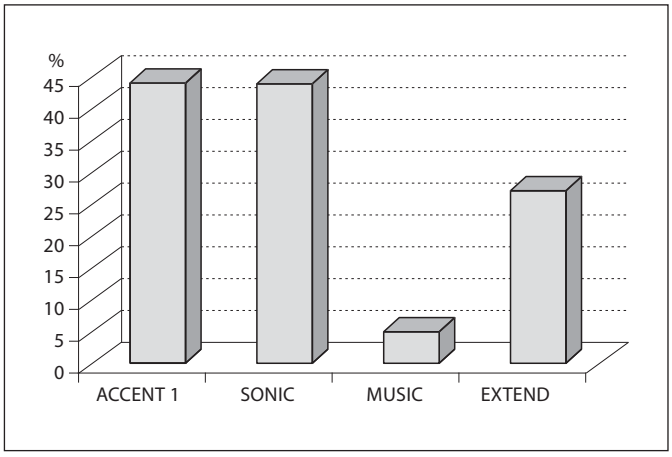

Fig. 1. Number (%) of CD patients achieving MH in clinical trials with anti-TNF agents.

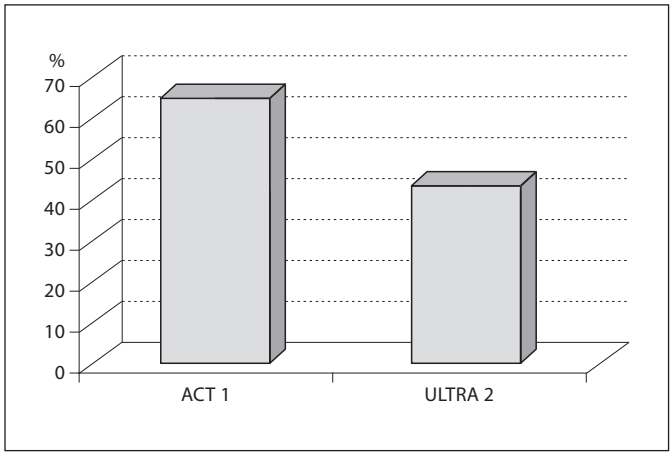

Fig. 2. Number (%) of UC patients achieving MH in clinical trials with anti-TNF agents.

demonstrated sustained MH in almost 50% of treated patients at 1 year. Moreover, a greater proportion of patients with scheduled treatment achieved complete MH at week 54 compared to the episodic group (50 vs. 7%, p = 0.007) [29]. D'Haens et al. [30], demonstrated that early induction therapy with infliximab combined with azathioprine maintenance therapy resulted in a greater rate of MH at 14 weeks (73.1%) when compared to the step-up approach with steroids and azathioprine (30,4%, p = 0.0028) [30]. In the EXTEND trial, a significant difference was observed in terms of MH at 1 year in the maintenance therapy group with adalimumab compared to the placebo group (24 vs. 0%, respectively) [9] (fig. 1).

In the postoperative setting, anti-TNF also allows maintenance of MH. In a randomized study, Regueiro et al. [31] studied 24 patients with CD who had undergone ileocolonic resection to receive intravenous infliximab, which was administered within 4 weeks of surgery and continued for 1 year, or placebo. The rate of recurrence (Rutgeerts score $\geq$i2) at 1 year was significantly lower in the infliximab group (9.1%) compared to the placebo group (84.6%, p = 0.0006) [31].

For UC, in the ACT-1 trial, scheduled maintenance therapy with infliximab 5 mg/kg every 8 weeks resulted in MH in 45.5% of patients compared to 18.2% ($p < 0.001$) in the placebo group at week 54 [25]. In the ULTRA 2 trial, MH in UC patients taking adalimumab every other week was achieved in 25 and 15.4% in the active arm and placebo group, respectively, (p = 0.032) at week 52 [28] (fig. 2).

Impact of Mucosal Healing on the Disease Course

Clinical Response/Remission

In the ACCENT 1 trial, patients who achieved MH with infliximab had a longer relapse-free disease course than those without MH [32]. Moreover, at week 54, a longer duration of clinical remission was observed in the complete MH group (20 weeks) compared to patients without complete MH (4 weeks) [32]. In a substudy of the ACCENT 1 trial, MH at weeks 10 and 54 was associated with higher clinical remission rates up to week 54, although these results were not statistically significant [29].

A substudy of the 'step-up/top-down' trial focused on the value of the endoscopic assessment after 2 years of treatment on clinical outcomes at years 3 and 4. MH (defined as an SES-CD score of zero) at 2 years predicted stable sustained clinical remission in the following 2 years in 68 versus 35% of patients (p = 0.004) with endoscopic evidence of persistent disease activity (defined as an SES-CD score from 2 to 9) [33]. In a large retrospective cohort study involving 214 CD patients on anti-TNF therapy, Schnitzler et al. [11] evaluated the impact of MH on long-term outcomes. At 5 years, clinical remission was maintained in 65% (83/128) of patients with MH compared to 40% (34/86) of patients who did not achieve MH (p = 0.0004) [11].

It has been demonstrated that the Rutgeerts score, which has become the gold standard for evaluating CD postoperative recurrence as the severity of endoscopic lesions at 1 year, is predictive of clinical recurrence [15]. A total of 89 CD patients who had been treated by ileal re-

section were included in a prospective cohort study [15]. Three years after surgery, the endoscopic recurrence rate was 85% and symptomatic recurrence occurred in 34% [15]. Endoscopic disease often recurs after infliximab is stopped. In a prospective cohort study of 12 consecutive patients on a postoperative infliximab regimen, treatment was stopped 3 years after surgery. Discontinuation of infliximab resulted in endoscopic recurrence at 4 months in 10 of 12 patients (83%) [34].

For UC, similar findings were reported in a landmark study from 1966 [35]. Indeed, 40% of UC patients who achieved MH after acute treatment with oral and rectal corticosteroids remained asymptomatic during a 1-year follow-up [35], whereas only 18% of patients who did not achieve MH after treatment remained asymptomatic during the same period [35]. In the ACT-1 and ACT-2 trials [25, 26], the proportion of patients in clinical remission at week 30 of therapy was 4-fold greater for patients with MH at week 8 (48.3 vs. 9.5%, respectively).

Overall, these findings suggest that MH is associated with both a higher clinical response and lower relapse rates in both CD and UC [36].

Hospitalizations

In the endoscopic substudy of the ACCENT I trial, patients achieving MH at both weeks 10 and 54 needed less CD-related hospitalizations (0%) compared to those with MH at only one of two visits (18.8%) or with no healing at either visit (28%) [29]. In a retrospective single-center cohort study evaluating the long-term outcome of infliximab in 214 patients with CD, patients who achieved MH needed hospitalization less frequently than patients who did not achieve it (42.2 vs. 59.3%, respectively, $p = 0.0018$) [11].

For UC, Ardizzone et al. [37] showed that no MH after the first course of corticosteroid therapy was associated with a more aggressive disease course. Indeed, after multivariate analysis, lack of MH was the only factor associated with negative outcomes at 5 years, including hospitalization (HR 3.634, 95% CI 1.556–8.485, $p = 0.0029$) [37].

Thus, MH is associated with lower hospitalization rates in both UC and CD [36].

Surgery

Extensive and deep ulcerations in CD patients predicted a more aggressive clinical course with increased rates of penetrating complications and surgery [38]. In a retrospective single-center cohort study, Schnitzler et al. [11] found that patients who had MH on an infliximab regimen needed less abdominal surgeries than those who did not achieve MH [14.1 (12/89) vs. 38.4% (33/86), respectively; $p < 0.0001$]. In a Norwegian population-based cohort study involving 458 IBD patients, a greater proportion of CD patients [11% (6/53)] who achieved MH at 1 year were able to avoid surgical resection over a period of 5 years compared to 20% (18/88) who were without MH at 1 year ($p = 0.10$) [39]. Regarding UC, 2% of patients with MH at 1 year needed a surgical resection in 5 years compared to 7% of patients without MH ($p = 0.02$) [39].

In a retrospective single-center study, Ferrante et al. [40] demonstrated that a longer colectomy-free survival was observed among UC patients who achieved MH (defined as a Mayo endoscopic subscore of 0 or 1) at week 4 or week 10.

Hence, MH is associated with a reduced need for surgery in both CD and UC [36].

Colorectal Cancer

In a case-control study of 68 UC patients and 136 matched controls, the histological inflammation score was the only independent risk factor for the development of colorectal neoplasia (OR 4.69, 95% CI 2.10–10.48, $p < 0.001$) [41].

In a subsequent study, the same authors showed that macroscopically normal endoscopic findings returned the 5-year cancer risk to that of the general population (OR 0.38, 95% CI 0.19–0.73, $p = 0.003$) [42]. Rubin et al. [43] also demonstrated a higher risk of cancer and dysplasia in UC patients with a higher inflammatory activity score (OR 2.73, 95% CI 1.44–5.18, $p = 0.002$). Gupta et al. [44] confirmed that histological inflammation over time was associated with the progression towards advanced neoplasia in UC (HR 3, 95% CI 1.4–6.3).

MH is thus associated with a lower risk of colorectal cancer in UC; for CD, such data are lacking [36].

Conclusion

The definition of MH is still under debate and no formal definition has been universally accepted. Except for CDEIS, all endoscopic indices still lack validation in both CD and UC. Anti-TNF therapy is the most potent drug class to induce and maintain MH in IBD. MH may change the natural course of the disease by decreasing the need for surgery and reducing hospitalization rates in both UC and CD. MH may also prevent the development of long-term disease complications, such as bowel damage in CD

and colorectal cancer in UC. Schnitzler et al. [11] showed that MH predicts long-term outcome with maintenance therapy with infliximab in CD. The need for surgery was significantly different between the groups with and without MH (14 and 38.4%, respectively, $p < 0.0001$). Interestingly, there was no difference between the groups with complete and partial MH (14 vs. 14.1%, respectively). Hence, further investigation is required in order to establish the degree of MH needed to change the course of disease.

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References

1 Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T: Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. Gastroenterology 1996;110:45–51.

2 Peyrin-Biroulet L, Lemann M: Review article: remission rates achievable by current therapies for inflammatory bowel disease. Aliment Pharmacol Ther 2011;33:870–879.

3 Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang YX, Lang YH, Marano CW, Strauss R, Oddens BJ, Feagan BG, et al: Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011; 141:1194–1201.

4 De Cruz P, Kamm MA, Prideaux L, Allen PB, Moore G: Mucosal healing in Crohn's disease: a systematic review. Inflamm Bowel Dis 2012;26:22977.

5 Feagan BG, Lemann M, Befrits R, Connell W, D'Haens G, Ghosh S, Michetti P, Ochsenkuhn T, Panaccione R, Schreiber, et al: Recommendations for the treatment of Crohn's disease with tumor necrosis factor antagonists: an expert consensus report. Inflamm Bowel Dis 2012;18:152–160.

6 Pineton de Chambrun G, Peyrin-Biroulet L, Lemann M, Colombel JF: Clinical implications of mucosal healing for the management of IBD. Nat Rev Gastroenterol Hepatol 2010; 7:15–29.

7 Fefferman DS, Farrell RJ: Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. Clin Gastroenterol Hepatol 2005;3:11–24.

8 Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Lofberg R, Modigliani R, Present DH, Rutgeerts P, Scholmerich J, Stange EF, et al: A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology 2002;122:512–530.

9 Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, Reinisch W, Kumar A, Lazar A, Camez A, et al: Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012;142:1102–1111.

10 Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao WH, et al: Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402–413.

11 Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P: Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15:1295–1301.

12 D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lemann M, Marteau P, Rutgeerts P, Scholmerich J, et al: A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007;132:763–786.

13 Mary JY, Modigliani R: Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989;30:983–989.

14 Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, et al: Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60: 505–512.

15 Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M: Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956–963.

16 Hebuterne X, Lemann M, Bouhnik Y, Dewit O, Dupas JL, Mross M, D'Haens G, Mitchev K, Ernault E, Vermeire S, et al: Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut 2012;23:23.

17 Efthymiou A, Viazis N, Mantzaris G, Papadimitriou N, Tzourmakliotis D, Raptis S, Karamanolis DG: Does clinical response correlate with mucosal healing in patients with Crohn's disease of the small bowel? A prospective, case-series study using wireless capsule endoscopy. Inflamm Bowel Dis 2008;14:1542–1547.

18 Gal E, Geller A, Fraser G, Levi Z, Niv Y: Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). Dig Dis Sci 2008;53:1933–1937.

19 Truelove SC, Witts LJ: Cortisone in ulcerative colitis: final report on a therapeutic trial. Br Med J 1955;2:1041–1048.

20 Feagan BG, Greenberg GR, Wild G, Fedorak RN, Pare P, McDonald JWD, Dube R, Cohen A, Steinhart AH, Landau, S, et al: Treatment of ulcerative colitis with a humanized antibody to the alpha(4)beta(7) integrin. N Engl J Med 2005;352:2499–2507.

21 Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative-colitis. A randomized study. N Engl J Med 1987;317:1625–1629.

22 Travis SPL, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lemann M, Lichtenstein GR, et al: Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut 2012;61:535–342.

23 Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao WH, et al: Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–1549.
24 Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, et al: Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–1395.
25 Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, et al: Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
26 Sandborn WJ, Colombel JF, Reinisch W, Feagan BG, Rachmilewitz D, Olson A, Johanns J, Travers S, Present D, Sands BE, et al: Infliximab induces and maintains mucosal healing in ulcerative colitis patients: the ACT trials. Am J Gastroenterol 2005; 100:S310-S.
27 Afif W, Leighton JA, Hanauer SB, Loftus EV, Faubion WA, Pardi DS, Tremaine WJ, Krane SV, Bruining DH, Cohen RD, et al: Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis 2009;15:1302–1307.
28 Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB: Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142: 257–U150.
29 Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao WH, Patel K, Wolf DC, Safdi M, Colombel JF, et al: Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc 2006;63:433–442.
30 D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, et al: Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008;371:660–667.
31 Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE, et al: Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136:441–450.
32 D'Haens G, Noman M, Baert F, Hiele M, Van Assche G, Daperno M: Endoscopic healing after infliximab treatment for Crohn's disease provides a longer time to relapse. Gastroenterology 2002;122:A-100.
33 Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, et al: Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology 2010;138: 463–468.
34 Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D: Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. Clin Gastroenterol Hepatol 2010;8:591–599.
35 Wright R, Truelove SR: Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. Am J Dig Dis 1966;11:847–857.
36 Peyrin-Biroulet L, Ferrante M, Magro F, Campbell S, Franchimont D, Fidder H, Strid H, Ardizzone S, Veereman-Wauters G, Chevaux JB, et al: Results from the 2nd Scientific Workshop of the ECCO (I): impact of mucosal healing on the course of inflammatory bowel disease. J Crohn Colitis 2011;5: 477–483.
37 Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, Marmo R, Massari A, Molteni P, Maconi G, et al: Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol 2011;9:483–U117.
38 Allez M, Lemann M, Bonnet J, Cattan P, Jian R, Modigliani R: Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol 2002;97:947–953.
39 Froslie KF, Jahnsen J, Moum BA, Vatn MH, IBSEN group: Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology 2007;133:412–422.
40 Ferrante M, Vermeire S, Fidder H, Schnitzler F, Noman M, Van Assche G, De Hertogh G, Hoffman I, D'Hoore A, van Steen K, et al: Long-term outcome after infliximab for refractory ulcerative colitis. J Crohn Colitis 2008;2:219–225.
41 Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, Williams C, Price A, Talbot I, Forbes A: Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004;126:451–459.
42 Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A: Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. Gut 2004;53:1813–1816.
43 Rubin DT, Huo D, Rothe JA: Increased inflammatory activity is an independent risk factor for dysplasia and colorectal cancer in ulcerative colitis: a case-control analysis with blinded prospective pathology review. Gastroenterology 2006;130:A2.
44 Gupta RB, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, Bodian C, Ullman T: Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology 2007;133:1099–1105.